

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 55440

Title: Establishment of a pattern recognition metabolomics model for diagnosis of hepatocellular carcinoma

Reviewer's code: 03812042

Position: Editorial Board

Academic degree: MSc, PhD

Professional title: Assistant Professor, Professor, Research Associate

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

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Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-03-19 09:42

Reviewer performed review: 2020-03-31 08:48

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this paper authors characterized the serum metabolome of hepatocellular carcinoma to develop a new metabolomics diagnosis model and identify novel biomarkers useful for hepatocellular carcinoma screening. They based on pattern recognition method and ultra-performance liquid chromatography-mass spectroscopy to characterize the serum metabolome of patients with hepatocellular carcinoma and cirrhosis, followed by sequential feature selection combined with linear discriminant analysis to process the multivariate data. The paper is interesting, however there are some points that may be clarified before the publication. 1- Pag 3, line 9: why hydroxypurine and purine? The authors may explain the role of these molecules in cirrhosis. 2- Table 2 of Significantly altered metabolites should be better described in the Results section. A scatter plot with Metabolite differences should be shown to facilitate the reading and to better explain the differences 3- The appropriate control in this analysis is patients with cirrhosis. Authors found that glutamic acid, kynurenic acid, vanillic acid, and hydroxypurine (Figure 5B) were higher in patients with HCC than in patients with cirrhosis. Why they show only hydroxypurine and purine in Figure 5? Also differences of these other molecules should be shown. 4- In the pattern recognition analysis for diagnosis of HCC the dataset was randomly split into a training set of 20 HCC samples and 20 cirrhosis samples and a validation set of 10 HCC samples and nine cirrhosis samples. The number of training set samples and the number of validation samples is too little and should be increased. 5- What happens if the dataset is again split in a new training set and validation set? Will be obtained the same results? 6- I have the impression that in the LDA model the differences are due only to Hydroxypurine and Proline. What happens if Hydroxypurine and Proline are excluded? 7- Pag 7, line 10: what scientist understand better about pathogenesis of HCC except of metabolic way? It

is not clear. 8- In the study, only the LDA test gave significant results about different metabolites between HCC and cirrhosis. It is enough to define the results of the paper?
9- In figure of Histopathological examination (HE staining), authors should include the negative control 10- In some sentences the English language need to be revised.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 55440

Title: Establishment of a pattern recognition metabolomics model for diagnosis of hepatocellular carcinoma

Reviewer's code: 02562387

Position: Peer Reviewer

Academic degree: BSc, PhD

Professional title: Doctor, Research Scientist

Reviewer's Country/Territory: Spain

Author's Country/Territory: China

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In view of a lack of suitable biomarkers for the diagnosis of hepatocellular carcinoma (HCC), authors develop a pattern recognition method based on the analysis of new metabolites identified from serum metabolites of a series of HCC patients. Proteome analysis was performed using ultra-performance liquid chromatography-mass spectrometry (UPLC-MS). Authors found that concentration of most metabolites were lower in patients diagnosed with HCC; although the levels of hydroxypurine were higher in patient cases. Authors have developed a model based on metabolic data that would be ideal for the discovery of new biomarkers that could be applied to HCC diagnosis.

General comments: The main results obtained by the authors is the definition of two models based on the metabolomes of three groups of patients. From the scientific point of view, these findings might have certain relevance, however the level of evidence achieved is not enough to consider that the results described are robust enough for being applied in a clinical context. Authors should do an effort in trying to describe better the results and highlight the relevant results omitting those descriptions that might lead to non-relevant information. Authors should clarify how the models have been constructed: using the whole proteome or with those metabolites that are differentially expressed between groups? In any case, the number of variables (metabolites) included in constructing the models is very high. From my view, the models proposed are quite complex and my feeling is that the sample size is too small to generate an accurate diagnostic tool (20 samples for the training set and 10 for the validation) and the risk of overfitting is presumably very high....Hence, It would be necessary to have an independent series of cases in order to validate these findings. Authors should justify that the sample size is sufficient to validate the models that they have generated.

Minor comments: - Abstract: *Authors should include the number and type of analyzed



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patients as well as the type of samples. *Define AFP *Check spelling errors *The conclusion of the abstract is not in line with the aim of the study and it should be accordingly modified. -Introduction: *Check references citations. - Material and Methods: *Patient and samples: was the study approved by an Ethical Committee? Did the patients sign an informed consent? Define the group of patients including the number of cases analyzed or belonging to each group; indicate the type of blood collection tube and the volume collected. *Data processing and statistical analysis: Figure 1. Use the figure legit to detail the process of the data analysis and include the number of cases analyzed in each group. -Results: *Figure 2: From my view this figure does not provide relevant information and I consider that it should be omitted in the main manuscript.